IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Berzofsky *et al.*
Application No. 10/532,374
Filed: April 21, 2005
Confirmation No. 4276
For: METHODS TO PREVENT TUMOR RECURRENCE BY BLOCKADE OF TGF-BETA
Examiner: Sheela J. Huff
Art Unit: 1643
Attorney Reference No. 4239-67016-02

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APPLICANTS' APPEAL BRIEF

This is an Appeal Brief filed under 37 C.F.R. § 41.37. A Notice of Appeal was received by the U.S. Patent and Trademark Office (USPTO) on November 23, 2009. Applicants hereby petition for a three-month extension of time for response, and submit the appropriate fee via EFS, making the Appeal Brief due on or before **April 23, 2010**. In accordance with 37 C.F.R. § 41.20(b)(2), this Appeal Brief is being filed together with the required fee of $540. If additional fees are required in connection with filing this Appeal Brief, please charge Deposit Account 02-4550.

Nine documents listed in the Evidence Appendix are submitted herewith.

I. REAL PARTY IN INTEREST

The real party in interest is The Government of the United States of America as represented by the Secretary of the Department of Health and Human Services, the assignee of record of the present application (Reel 017330, Frames 0232-0238, recorded on April 21, 2005).

II. RELATED APPEALS AND INTERFERENCES

There are no related proceedings.

III. STATUS OF CLAIMS

Claims 46-72 are pending. Claims 1-45 have been canceled. Claims 46-72 have been rejected, and are appealed.

IV. STATUS OF AMENDMENTS

No amendment was filed in response to the Final Office Action of August 21, 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention stems from the discovery that a monoclonal antibody obtained from hybridoma 1D11.16 (hereinafter the "1D11.16 antibody"), which specifically neutralizes three isoforms of TGF-β (TGF-β1, TGF-β2, and TGF-β3), inhibits tumor recurrence *in vivo*. Applicants demonstrated that mice inoculated with the 1D11.16 anti-TGF-β antibody were protected from local tumor recurrence, but not from primary tumor growth. As embodied by claim 46, the invention at issue relates to a method of *inhibiting recurrence* of a tumor in a subject by "administering a therapeutically effective amount of a monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849), or a humanized equivalent thereof, to the subject in order to block an immunosuppressive effect of transforming growth factor (TGF)-β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the monoclonal antibody or humanized antibody is specific for TGF-β and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject." See the specification, for example, at page 7, lines 17-19; page 8, lines 5-14; and page 18, lines 17-28.

As further embodied by claim 60, the invention at issue relates to a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor by "contacting a TGF-β receptor-expressing immune cell with an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, or a humanized equivalent thereof, wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased activity of the immune cell, wherein the increased activity is increased tumor immunosurveillance, thereby enhancing the activity of the immune cell to inhibit recurrence of the tumor." See the specification, for example, at page 7, lines 17-19; page 8, lines 5-14; and page 19, lines 23-37.

In a further embodiment, as exemplified by claim 63, the invention at issue relates to a method of enhancing an immune response in a subject to inhibit recurrence of a tumor by "administering to the subject a therapeutically effective amount of an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, or a humanized equivalent thereof, wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance in the subject, thereby enhancing the immune response in the subject to inhibit recurrence of a tumor." See the specification, for example, at page 7, lines 17-19; page 8, lines 5-14; and page 20, lines 1-15.

VI. GROUND OF REJECTION FOR REVIEW

Claims 46-50, 52-55, 59-67, 69, and 71 are rejected under 35 U.S.C. §103(a) as allegedly unpatentably obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of PCT Application No. WO 00/01410, Barbera-Guillem (U.S. Patent No. 6,224,866), Rosenblum (U.S. Patent Application No. 2005/0214307), and Zavada *et al.* (U.S. Patent No. 6,297,041).

Claims 46-55 and 59-72 are rejected under 35 U.S.C. §103(a) are rejected as allegedly being unpatentable over Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333).

Claims 46-72 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000).

Applicants strenuously traverse these rejections.

VII. ARGUMENT

A. Rejection of Claims 46-50, 52-55, 59-67, 69, and 71 under 35 U.S.C. § 103(a)

Claims 46-50, 52-55, 59-67, 69, and 71 are rejected under 35 U.S.C. §103(a) as allegedly unpatentably obvious over Dasch *et al.* in view of PCT Application No. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.*

(1)The Cited References

Dasch *et al.* (i) discloses the use of a TGF-beta antagonist (the 1D11.16 anti-TGF-beta antibody) or a humanized equivalent (column 2, lines 49-52) to *regress existing tumors* (column 5, lines 54-58), to *treat* tumor cells that produce TGF-beta (column 2, lines 28-32), and to *treat* metastatic cancers (column 2, lines 33-37), and (ii) claims a method of inhibiting the growth of tumor cells (claim 1). Dasch *et al.* does not teach the use of the disclosed TGF-beta antagonists to *inhibit the recurrence* of a tumor, nor could this be inferred from the reference. In this regard, Dasch *et al.* does not disclose the concept of tumor recurrence, nor would it be known from the teachings of Dasch *et al.* that the disclosed TGF-beta antagonists could inhibit tumor recurrence. Nor does Dasch *et al.* disclose a method of enhancing an activity of an immune cell or a method of enhancing an immune response in a subject to inhibit recurrence of a tumor.

Barbera-Guillem discloses the use of an immunotherapeutic composition that binds directly to B cells (for example, anti-CD20, anti-Lym-1, or anti-CD19 antibodies) in order to cause B cell depletion and reduce a pro-tumor immune response (see for example, column 3, line 1 through column 4, line 14; column 5, lines 57-63). Barbera-Guillem also discloses that the same agent can be used to *treat* both a primary tumor and a recurrence. However, Barbera-Guillem does not teach that the disclosed agents can *inhibit* tumor recurrence, nor does it teach anything about the 1D11 antibody or any antibody that can bind soluble TGF-beta. Nor does Barbera-Guillem disclose a method of enhancing an activity of an immune cell or a method of enhancing an immune response in a subject to inhibit recurrence of a tumor.

WO 00/01410 discloses "that antagonizing the effects of TGF-β1 suppresses tumor growth *in vivo* through an anti-angiogenic mechanism" (WO 00/01410, page 3, lines 19-20). WO 00/01410 also discloses that the anti-TGF-beta antibodies can be used "to detect or quantify

the TGF-β" and that the "[r]esults from these tests can be used to diagnose or predict the occurrence of recurrence of a cancer" (WO 00/01410, page 24, lines 7-9). However, there is no teaching in WO 00/01410 that anti-TGF-beta antibodies can be used to *treat* or *inhibit* tumor recurrence and it does not teach the 1D11.16 antibody, nor is there any teaching of a method of enhancing an activity of an immune cell or of enhancing an immune response in a subject to inhibit recurrence of a tumor.

Zavada *et al.* discloses the use of antibodies directed against an oncoprotein (the MN protein) to *treat* (not inhibit tumor recurrence in) cancer patients abnormally expressing the MN protein (column 10, lines 25-44). Zavada *et al.* also discloses the use of the MN protein or an anti-idiotypic antibody (as a surrogate antigen or antigen mimic) as a vaccine in a method of *inhibiting recurrence* of a MN-expressing tumor (paragraph bridging columns 10 and 11). Zavada *et al.* does not disclose the 1D11.16 antibody, or any anti-TGF-beta antibody, that inhibits tumor recurrence. Zavada *et al.* also does not disclose a method of enhancing an activity of an immune cell or of enhancing an immune response in a subject to inhibit recurrence of a tumor.

Rosenblum discloses that one specific agent (an immunoconjugate comprised of a single chain antibody linked to a cytotoxic moiety, where the antibody moiety recognizes the cell surface protein GP 240 and thereby targets the cytotoxic moiety to a tumor cell expressing this antigen) used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The sole purpose of the antibody moiety in the Rosenblum agent is to target the cytotoxin (the active, anti-tumor component of the immunoconjugate) to the GP 240-expressing tumor cell (paragraph [0015]). In fact, the antibody alone had no inhibitory effect on tumor growth (paragraphs [0134] and [0136]). Thus, the "antibody" disclosed in Rosenblum is not, *per se*, preventing the tumor recurrence; it is simply acting as a vehicle to target the anti-tumor cytotoxin to the tumor cell. Rosenblum does not disclose the 1D11.16 antibody or any another antibody that inhibits TGF-beta activity. Nor does Rosenblum disclose a method of enhancing an activity of an immune cell or a method of enhancing an immune response in a subject to inhibit recurrence of a tumor.

(2) Claims are directed to a method of inhibiting tumor recurrence

Applicants emphasize that the claims are directed to methods of *inhibiting* a tumor *recurrence* and not to methods of *treating* a tumor or *treating* a tumor *recurrence*, and that treating and inhibiting are two very different actions. As discussed in the Declaration under 37 C.F.R. 1.132 of Inventor Jay A. Berzofsky, M.D., Ph.D., dated June 5, 2009 (hereinafter the "June 5, 2009 Declaration"), "the actions of "inhibiting" and "treating" are very different, as methods of inhibiting a tumor recurrence are prophylactic and are used to prevent a tumor from *developing*, whereas methods of treating a tumor recurrence are directed against an *existing* tumor" (June 5, 2009 Declaration at paragraph 3).

(3) Primary tumors, metastatic (secondary) tumors, and recurrent tumors

This section provides general information regarding types of tumors. Applicants note there are recognized biological differences between original (primary) tumors, recurrent tumors, and metastatic (secondary) tumors. "Specifically, a tumor recurrence is the return of a tumor, at the same site as the original (primary) tumor, after the tumor has been removed surgically, by drug or other treatment, or has otherwise disappeared. A tumor recurrence is not a metastasis, as a metastasis is the spread of a tumor from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in the original (primary) tumor. There can be a recurrence of either a primary tumor or a metastasis. Cells of a recurrent primary tumor or a recurrent metastatic tumor can arise by escape from anti-tumor immune responses and differ from the original primary tumor by having loss of a tumor antigen, mutation of a tumor antigen, or loss or decreased expression of Major Histocompatibility Complex (MHC) molecules presenting the tumor antigens. Tumors that recur after chemotherapy usually do so by development of mutations or other changes resulting in resistance to the chemotherapy agent used" (paragraph 4 of the Declaration under 37 C.F.R. 1.132 of Inventor Jay A. Berzofsky, M.D., Ph.D. dated March 10, 2008; hereinafter the "March 10, 2008 Declaration").

(4) Inhibiting* versus *treating

(i) Specification does not equate treatment to inhibition

The Office action dated May 12, 2008, alleges that because "[A]pplicant defines treatment as including prophylactic inhibition," Applicant therefore "equates treatment to inhibition/prevention" (May 12, 2008 Office action at pages 4 and 5). Applicants disagree and respectfully pointed out in the Amendment and Response dated June 11, 2009, that the "generic word 'treatment' is an all-purpose term that refers to many things, including the use of both agents and therapies to inhibit or treat a disease in a subject" (June 5, 2009 Declaration at paragraph 4). The specification at page 17, lines 11-14, states that treatment "[r]efers to **both** prophylactic inhibition of disease (such as tumor recurrence) and therapeutic interventions to alter the natural course of an untreated disease process, such as a tumor growth. Treatment of a tumor **includes**, for instance, the surgical removal of the tumor. Treatment of a tumor can also **include** chemotherapy, immunotherapy, or radiation therapy. Two or more methods of treating a tumor can be provided to a subject in combination. Treatment of a subject **includes** inhibiting or measurably reducing the recurrence of a tumor" (emphasis added). "As treatment encompasses both inhibition and intervention, treatment **cannot be equated exclusively** with inhibition" (June 5, 2009 Declaration at paragraph 4; emphasis added). Thus, Applicants strenuously submitted (and maintain) that the specification does not define *treatment* as being equivalent to *inhibition*, nor should the Office interpret that Applicants believe that these terms are equivalent. Applicants thank the Examiner for acknowledging in the Office action dated August 21, 2009, that Applicants have "clearly discussed inhibiting is only a part of treating" (August 21, 2009 Office action at page 4).

(ii) Therapeutically effective amount of an agent for treatment *versus* inhibition

The Office action dated May 12, 2008 also alleges that the "definition of 'therapeutically effective amount of an agent' gives an example of using the same anti-TGF-beta antibody to treat and inhibit tumor recurrence (see page 16, lines 32-33)" (May 12, 2008 Office action at page 5). Applicants disagree and respectfully pointed out in the Amendment and Response dated June 11, 2009, that the Office had unnecessarily narrowly interpreted this passage from the specification. The statement that "the amount of neutralizing anti-TGF-β antibody that, when administered to a subject following treatment of a tumor, can inhibit recurrence of the tumor"

(specification at page 16, lines 32-33) is not a statement that the neutralizing anti-TGF-β antibody itself is administered to treat an existing tumor. Rather, the point of the statement is to acknowledge that the neutralizing anti-TGF-β antibody can be used to inhibit recurrence of the tumor following any treatment of a tumor (for example, surgery, chemotherapy, immunotherapy, radiation therapy *etc.*). Accordingly, the cited passage does not support the Office's assertion that Applicants have equated treatment exclusively with inhibition. Applicants thank the Examiner for acknowledging in the Office action dated August 21, 2009, that "the intent of the passage was to be that the neutralizing antibody can be used to inhibit reoccurrence following any treatment of a tumor" (Office action at page 4).

However, the August 21, 2009 Office action alleges that "it seems applicant is implying that the antibody of the invention can only inhibit tumor recurrence after previous treatment and as shown by Dasch, . . . the same antibody can also be used in treatment" (Office action at page 4). Applicants agree that the antibody of the invention inhibits tumor recurrence after a previous treatment, because in order for recurrence to take place, the original, primary tumor must be removed using some kind of treatment (for example, surgery, chemotherapy, immunotherapy, radiation therapy *etc.*). Applicants also agree that Dasch *et al.* teaches that the antibody of the invention can be used to treat a tumor. However, Dasch *et al.* does not teach that the 1D11.16 antibody can be used to treat tumor *recurrence*, which fact has been repeatedly acknowledged by the Examiner (see Office actions dated November 8, 2007 at page 5 and February 11, 2009 at page 4), nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence. Thus, "treatment," within the context of the disclosure of Dasch *et al.*, does not read on "inhibition of tumor recurrence." Moreover, it is well known in the art that "the effectiveness of an agent for *treating* a tumor recurrence does not predict the effectiveness of the same agent for *inhibiting* the recurrence" (June 5, 2009 Declaration at paragraph 3; see also June 5, 2009 Declaration at paragraphs 5 and 6). Thus, even if Dasch *et al.* had suggested using the 1D11.16 antibody for treating tumor recurrence (which it does not), this antibody would not have been expected to be effective at inhibiting tumor recurrence, based on what was already known in the art at the time the application was filed.

(5) The Rejection* Vis-à-Vis *the Cited References

(i) Claims 46-50, 52-55, 59, 67, and 68

Claims 46-50, 52-55, 59, 67, and 68 are rejected under 35 U.S.C. §103(a) as allegedly unpatentably obvious over Dasch *et al.* in view of PCT Application No. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* In order to support a conclusion that a claimed invention is obvious, the USPTO must show (i) that all the claimed elements were known in the prior art and (ii) that combining the elements would have yielded predictable results to one of skill in the art. Thus, once it is determined that all of the claimed elements are present in the prior art, the predictability of the claimed combination can be addressed. With regard to the latter, the USPTO has provided Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* Based on those Guidelines, the Office must provide the appropriate rationale to support rejections under 35 U.S.C. §103. More specifically, the Guidelines provide the following non-exclusive rationales for supporting a finding that a claimed invention is obvious (with emphasis added):

(A) combining prior art elements according to known methods to yield **predictable** results;

(B) simple substitution of one known element for another to obtain **predictable** results;

(C) use of **known** technique to improve similar devices (methods, or products) in the same way;

(D) applying a **known** technique to a known device (method, or product) ready for improvement to yield **predictable** results;

(E) "obvious to try" - choosing from a finite number of identified, **predictable** solutions, **with a reasonable expectation of success**;

(F) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been **predictable** to one of ordinary skill in the art; and

(G) some **teaching, suggestion, or motivation** in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The emphasis in the Guidelines is accordingly the **predictability** of the combination, as a basis for a finding that there is a reasonable expectation of success of obtaining the Applicants'

invention associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of references, and accordingly no reasonable expectation of success. Thus, claims 46-50, 52-55, 59, 67, and 68 are allowable.

(a) The cited references do not teach all of the elements of the claimed invention

Applicants submit that the cited references do not teach all of the elements of the claimed invention (they do not make up for the deficiencies of Dasch *et al.*). As acknowledged in the Office actions dated November 8, 2007, and February 11, 2009, Dasch *et al.* does not discuss the treatment of tumor recurrence (nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence). Dasch *et al.* is combined with four other references (WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.*) that allegedly make up for the deficiency of Dasch *et al.* Applicants respectfully disagree. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* each disclose antibodies, but that is where the similarity with Applicants' claimed methods ends.

WO 00/01410 discloses the use of anti-TGF-beta antibodies "to detect or quantify the TGF-β" and that the "[r]esults from these tests can be used to diagnose or predict the occurrence or recurrence of a cancer" (WO 00/01410, page 24, lines 7-9; emphasis added). WO 00/01410 does not disclose that the anti-TGF-beta antibodies can be used to inhibit tumor recurrence. Thus, specifically with regard to inhibition of tumor recurrence, WO 00/01410 teaches using anti-TGF-beta antibodies in a diagnostic method, but not a therapeutic method. WO 00/01410 does not disclose the 1D11.16 antibody or a humanized equivalent thereof.

Barbera-Guillem discloses the use of an immunotherapeutic composition that binds directly to B cells (for example, anti-CD20, anti-Lym-1, or anti-CD19 antibodies) in order to cause B cell depletion and reduce a pro-tumor immune response (see for example, column 3, line 1 through column 4, line 14; column 5, lines 57-63). Barbera-Guillem does not teach the 1D11.16 antibody or a humanized equivalent thereof, nor does it teach any other antibody that can bind soluble TGF-beta. In contrast to the antibodies disclosed in Barbera-Guillem, the 1D11.16 antibody of the claimed method does not bind B cells or deplete B cells; rather, it binds TGF-beta which is released from non-T-non-B cells (see, for example, the specification at page 31, lines 26-29). More specifically, the 1D11 antibody blocks an immunosuppressive effect of

TGF-beta in order to increase immunosurveillance by B cells or T cells (see, for example, page 19, lines 23-32 and Example 5). In other words, the 1D11.16 antibody acts to increase the biological activity of B cells and T cells, whereas the antibody disclosed in Barbera-Guillem effectively acts to decrease the biological activity of B cells by depleting them. As the antibodies disclosed in Barbera-Guillem function by a completely different mechanism than the 1D11.16 antibody, Barbera-Guillem teaches away from using an antibody to increase the biological activity of B cells and T cells.

Rosenblum discloses that one specific agent used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The "agent" of Rosenblum is an immunoconjugate comprised of a monoclonal antibody or a single chain antibody linked to a cytotoxic moiety, where the antibody moiety recognizes the cell surface protein GP 240 and thereby targets the cytotoxic moiety to a tumor cell expressing this antigen (paragraph [0013]). The sole purpose of the antibody moiety is to target the cytotoxin (the active, anti-tumor component of the immunoconjugate) to the GP 240-expressing tumor cell (paragraph [0015]). In fact, the antibody alone had no inhibitory effect on tumor growth (paragraphs [0134] and [0136]). Thus, the "antibody" disclosed in Rosenblum is not, *per se*, inhibiting the tumor recurrence; it is simply targeting the anti-tumor cytotoxin to the tumor cell. Rosenblum does not disclose the 1D11.16 antibody or another antibody that inhibits TGF-beta activity (for example, a humanized equivalent of the 1D11.16 antibody).

Zavada *et al.* discloses the use of antibodies directed against an oncoprotein (the MN protein) to *treat* cancer patients expressing the MN protein (column 10, lines 42-44). Zavada *et al.* also discloses the use of a different agent, anti-idiotype antibodies to MN-specific antibodies (mimics of the MN protein), in a vaccine to *inhibit recurrence* of a MN-expressing tumor (column 11, lines 5-9). Zavada *et al.* does not teach that one specific agent can be used to both treat a tumor and inhibit a recurrence, nor does Zavada *et al.* disclose the 1D11.16 antibody or another antibody that inhibits TGF-beta activity (for example, a humanized equivalent of the 1D11.16 antibody).

In view of the above, Applicants respectfully submit that as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* teach that an anti-TGF-beta antibody, and more specifically the 1D11.16 antibody or its humanized equivalent, can inhibit tumor recurrence, the

cited references do not make up the deficiencies of Dasch *et al.* and therefore the references do not teach **all of the elements** of the claimed invention.

(b) Combining the elements would not have yielded ***predictable*** *results to one of skill in the art*

If it is determined that all of the claimed elements are, in fact, present in the prior art (as discussed above, Applicants do not believe this to be true), the predictability of the claimed combination can be addressed. The Office action dated February 11, 2009 alleges that "[b]ecause it is well known in the art to use the same antibody used in treatment of a tumor as in the treatment of tumor recurrence, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the antibody of the primary reference in the treatment of tumor recurrence" (Office action at page 5). Applicants disagree and respectfully submit that the teachings of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* could not have been combined to **predictably** yield the claimed invention.

As discussed above, "the actions of "inhibiting" and "treating" are very different, as methods of inhibiting a tumor recurrence are prophylactic and are used to prevent a tumor from *developing*, whereas methods of treating a tumor recurrence are directed against an *existing* tumor" (June 5, 2009 Declaration at paragraph 3). Also as discussed above, the specification does not define *treatment* as being equivalent to *inhibition* and the Examiner has acknowledged in the Office action dated August 21, 2009, that Applicants have "clearly discussed inhibiting is only a part of treating" (August 21, 2009 Office action at page 4). Thus, although a document may disclose that an agent can be used in the "treatment" of a tumor (or even treatment of a tumor recurrence), unless the document specifically discloses that the same agent can be used to *inhibit* tumor *recurrence*, it does not teach that an agent used to treat tumor recurrence also inhibits tumor recurrence. That it is also well known in the art that antibodies are unpredictable, further emphasizes that the use of an antibody for one purpose (treatment) does not predict its use for an entirely different purpose (inhibition).

WO 00/01410 discloses that the anti-TGF-beta antibodies can be used "to detect or quantify the TGF-β" and that the "[r]esults from these tests can be used to diagnose or predict the occurrence of recurrence of a cancer" (WO 00/01410, page 24, lines 7-9; emphasis added). Thus, this reference teaches that the antibody can be used to quantify the amount of TGF-beta as a measure of potential recurrence, rather than using the disclosed antibody to inhibit tumor

recurrence. The Office action dated February 11, 2009, alleges that simply because WO 00/01410 discloses that antibodies directed against TGF-beta can "be used in the diagnosis and treatment of proliferating cells and that the diagnosis also includes diagnosing tumor recurrence . . . one of ordinary skill in the art would immediately envisage that the same antibody that can detect tumor recurrence can also be used in treatment of tumor recurrence" (February 11, 2009 Office action at page 5). The Office action dated August 21, 2009, alleges that given that the WO 00/01410 antibody "is known to be used in treatment and diagnosis of tumors and known to be used in diagnosis of tumor recurrence, one skilled in the art would logically envisage the treatment of tumor recurrence" (8/21/09 Office action at page 5). Applicants strenuously disagree. It is well known in the art that "antibodies are unpredictable" (June 5, 2009 Declaration at paragraph 7) and it is not predictable that an agent used to **measure or predict** a tumor or a tumor recurrence will be effective at **inhibiting** a tumor recurrence. A clear example is that "antibodies to Prostate Specific Antigen (PSA) can be used to measure PSA levels to monitor tumor progression or detect or predict tumor recurrence, but these anti-PSA antibodies cannot be used to treat, prevent, or inhibit tumor recurrence" (June 5, 2009 Declaration at paragraph 7). Thus, it would not be predictive, and one of skill in the art would not immediately or logically envisage, that an antibody used to **treat** a tumor or a tumor recurrence would be effective at **inhibiting** a tumor recurrence. Similarly, "one of skill in the art would not be able to predict that an antibody used for **detection and treatment** also would be effective at **inhibition** of tumor recurrence, without first having demonstrated that the antibody can function to both detect and inhibit (or even treat) tumor recurrence" (June 5, 2009 Declaration at paragraph 7; emphasis added), nor would one of skill in the art equate "detection" with "inhibition."

As discussed above, the antibodies disclosed in Barbera-Guillem function by a completely different mechanism than the 1D11.16 antibody and Barbera-Guillem teaches away from using an antibody to increase the biological activity of B cells and T cells. Accordingly, the antibodies disclosed in Barbera-Guillem provide no reliable guidance for the activities exhibited by the 1D11.16 antibody, nor are they at all **predictive** of Applicants' use of this antibody or its humanized equivalent.

Zavada *et al.* discloses the use of antibodies directed against an oncoprotein (the MN protein) to *treat* cancer patients expressing the MN protein (column 10, lines 42-44). Zavada *et al.* also discloses the use of a different agent, anti-idiotype antibodies to MN-specific antibodies

(mimics of the MN protein), in a vaccine to *inhibit recurrence* of a MN-expressing tumor (column 11, lines 5-9). As Zavada *et al.* does not teach that one specific agent can be used to both treat a tumor and inhibit a recurrence, one of skill in the art **would not have predicted** the claimed method in view of this reference.

Rosenblum discloses that one specific agent (an immunoconjugate comprised of a monoclonal antibody or a single chain antibody linked to a cytotoxic moiety, where the antibody moiety recognizes the cell surface protein GP 240 and targets the cytotoxic moiety to a tumor cell) used in the treatment of tumors can be used to prevent tumor recurrence. Rosenblum does not disclose the 1D11.16 antibody or another antibody that inhibits TGF-beta activity. The mere fact that Rosenblum (or any reference) discloses an antibody that targets a tumor protein is, on its own, not predictive of Applicants' claimed method, which uses a completely different antibody in an unpredicted application. In contrast to the agent of the Rosenblum disclosure, the anti-TGF-beta antibody of the claimed method does not target the tumor cell at all, but rather removes an inhibitor that is blocking an immune response. Thus, it would be overstating the reference and, at a minimum, a stretch to say that Rosenblum teaches that the antibody itself is used for treatment of tumors. Accordingly, nothing about the Rosenblum agent would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11.16 antibody or its humanized equivalent, nor is it **predictive** in any way of Applicants' specific use of this antibody to inhibit tumor recurrence.

None of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants use of the specific 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence. Thus, the combined teachings of these references with Dasch *et al.* (which does not teach inhibition, or treatment, of tumor recurrence) could not have **predictably** yielded the claimed invention and there is no basis for the Office's assertion that claims 46-50, 52-55, 59, 67, and 68 are obvious.

(c) There is no reasonable expectation of success in combining the references

For a *prima facie* case of obviousness, the prior art must support a reasonable expectation of success for achieving the invention. "The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a *reasonable expectation* of success." M.P.E.P. § 2143.02 (emphasis added). The references cited in the rejection of claims 46-50, 52-55, 59, 67,

and 68 under 35 U.S.C. § 103(a) do not support a reasonable expectation of success for achieving the claimed invention, and in fact, with regard to Barbera-Guillem, teach away from the claimed invention. Therefore, the Office has not met this requirement for establishing *prima facie* obviousness, and claims 46-50, 52-55, 59, 67, and 68 are allowable.

The Office action dated February 11, 2009 alleges that "WO 00/01410 discloses that antibodies against TGF-beta can be used in the treatment and diagnosis of proliferating cells and that these antibodies can also be used to detect tumor recurrences (see pages 23-24). Barbera-Guillem discloses that one skilled in the art would readily recognize that the same procedure used for treating cancer would also be used for the treatment of recurrence of the same cancer (col. 23, lines 20-25). It is also that the reference discloses antibody therapy, which is the same type of therapy used by applicant. Rosenblum discloses that the same antibody used in treatment of tumors is used in the treatment of tumor recurrence (paragraph [0043]). Zavada *et al.* discloses the same compounds (which include polypeptides and antibodies) can be used for treatment and treatment of recurrence (col.10, line 50 to col. 11, line). Thus, the use of the same antibody in treatment of tumors is also used in the treatment of recurrent tumors" (Office action at the paragraph bridging pages 4 and 5). Applicants disagree.

First, as discussed above, claims 46-50, 52-55, 59, 67, and 68 are directed to methods of *inhibiting* a tumor *recurrence* and <u>not</u> to *treating* a tumor or *treating* a tumor *recurrence*. Also, as discussed above, the actions of "inhibiting" and "treating" are very different. Thus, the statement that "the use of the same antibody in treatment of tumors is also used in the treatment of recurrent tumors" does not apply to the claimed invention.

Second, Barbera-Guillem, WO 00/01410, Zavada *et al.*, and Rosenblum all disclose antibodies, but not the 1D11.16 antibody or its humanized equivalent. Dasch discloses that the 1D11.16 antibody can be used treat a tumor, but does not disclose that the 1D11.16 antibody can be used to treat or inhibit a tumor recurrence. As antibodies are biological molecules and are inherently unpredictable, there would be no reasonable expectation of success that replacing the antibodies disclosed in Barbera-Guillem, WO 00/01410, Zavada *et al.*, and Rosenblum with the 1D11.16 antibody would successfully lead to the use of the 1D11.16 antibody, or its humanized equivalent, to inhibit tumor recurrence. Moreover, there is no teaching in Barbera-Guillem, WO 00/01410, Zavada *et al.*, and Rosenblum either alone or in combination which would lead one of skill in the art to reasonably expect that an anti-TGF-beta antibody, which was previously used to

treat tumors (Dasch *et al.*) would be successful at inhibiting tumor recurrence, as recited in the claims.

In view of the above discussion, one of skill in the art would not have had a reasonable expectation of success, based on the disclosures of Barbera-Guillem, WO 00/01410, Zavada *et al.*, or Rosenblum, that the 1D11.16 antibody disclosed in Dasch *et al.* or its humanized equivalent could be used to inhibit tumor recurrence. Therefore, the Office has not met its burden of showing a **reasonable expectation of success** for achieving the claimed invention to support the rejection of claims 46-50, 52-55, 59, 67, and 68 as obvious.

(d) Summary

Applicants respectfully submit that as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* teach that any anti-TGF-beta antibody, and more specifically the 1D11.16 antibody or its humanized equivalent, can inhibit tumor recurrence, the cited references do not make up the deficiencies of Dasch *et al.* and therefore the references do not teach **all of the elements** of the claimed invention. None of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* is predictive of Applicants' use of the specific 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence. Thus, the combined teachings of these references and Dasch *et al.* (which does not teach inhibition, or treatment, of tumor recurrence) could not have **predictably** yielded the claimed invention. Moreover, combining the references does not provide a **reasonable expectation of success** that the 1D11.16 antibody, or its humanized equivalent, would be effective at inhibiting tumor recurrence. Accordingly, Applicants submit that claims 46-50, 52-55, 59, 59, 67, and 68 are allowable.

(ii) Claims 60-62, and 69

Claims 60-62, and 69 are rejected under 35 U.S.C. §103(a) as allegedly unpatentably obvious over Dasch *et al.* in view of PCT Application No. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are discussed above (see Sections (1) and (5)(i)). It is also discussed in detail above (Section (5)(i)) that in order to support a conclusion that a claimed invention is obvious, the USPTO must show (i) that all the claimed elements were known in the prior art and (ii) that combining the elements would have yielded predictable results to one of skill in the art. The

emphasis in the Guidelines is accordingly the predictability of the combination, as a basis for a finding that there is a reasonable expectation of success of obtaining the Applicants' invention associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of references, and accordingly no reasonable expectation of success. Thus, claims 60-62, and 69 are allowable.

Claim 60 (and claims 61, 62, and 69 dependent therefrom) are directed to:

- a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor;
- contacting a TGF-β receptor-expressing immune cell with an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, or a humanized equivalent thereof, wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased activity of the immune cell;
- wherein the increased activity is increased tumor immunosurveillance.

Claim 60 recites, in part, "wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased activity of the immune cell." Applicants submit that the claim elements recited in this statement are an inherent property of the 1D11.16 antibody and its humanized equivalent, which is extensively discussed above in Section (5)(i) with respect to this rejection. To summarize the remarks presented above, none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* teach that an anti-TGF-beta antibody, and more specifically the 1D11.16 antibody or its humanized equivalent, can inhibit tumor recurrence. Therefore, these references do not make up the deficiencies of Dasch *et al.* and together they do not teach all of the elements of the claimed invention. None of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* is predictive of Applicants use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence, and the combined teachings of these references with Dasch *et al.* could not have predictably yielded the claimed invention, nor would it have provided a reasonable expectation of success that the 1D11.16 antibody, or its humanized equivalent, would be effective at inhibiting tumor recurrence.

It is further submitted, with respect to claims 60-62, and 69, that none of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* disclose a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody, its humanized equivalent, or any anti-TGF-beta antibody, wherein the increased activity is increased tumor immunosurveillance. Thus, these references do not teach **all of the elements** of the claimed invention. Moreover, as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants' use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence (see Section (5)(i)(b) above), these references, when combined with Dasch *et al.*, similarly would not be **predictive** of the claimed method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody. Nor would combining these references provide any **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an activity of an immune cell to inhibit recurrence of a tumor. Accordingly, Applicants submit that claims 60-62, and 69 are allowable.

(iii) Claims 63-66 and 71

Claims 63-66 and 71 are rejected under 35 U.S.C. §103(a) as allegedly unpatentably obvious over Dasch *et al.* in view of PCT Application No. WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are discussed above (see Sections (1) and (5)(i)). It is also discussed in detail above (Section (5)(i)) that in order to support a conclusion that a claimed invention is obvious, the USPTO must show (i) that all the claimed elements were known in the prior art and (ii) that combining the elements would have yielded predictable results to one of skill in the art. The emphasis in the Guidelines is accordingly the predictability of the combination, as a basis for a finding that there is a reasonable expectation of success of obtaining the Applicants' invention associated with a prior art combination. It is respectfully submitted that in the present case, there is no such element of predictability in the purported combination of references, and accordingly no reasonable expectation of success. Thus, claims 63-66 and 71 are allowable.

Claim 63 (and claims 64-66 and 71dependent therefrom) are directed to:

- a method of enhancing an immune response in a subject to inhibit recurrence of a tumor;

- administering to the subject a therapeutically effective amount of an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, or a humanized equivalent thereof, wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway;
- wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance in the subject.

Claim 63 recites, in part, "wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway." Applicants submit that the claim elements recited in this statement are an inherent property of the 1D11.16 antibody and its humanized equivalent, which is extensively discussed above in Section (5)(i) with respect to this rejection. To summarize the remarks presented above, none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* teach that an anti-TGF-beta antibody, and more specifically the 1D11.16 antibody or its humanized equivalent, can inhibit tumor recurrence. Therefore, these references do not make up the deficiencies of Dasch *et al.* and together they do not teach all of the elements of the claimed invention. None of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* is predictive of Applicants use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence, and the combined teachings of these references with Dasch *et al.* could not have predictably yielded the claimed invention, nor would it have provided a reasonable expectation of success that the 1D11.16 antibody, or its humanized equivalent, would be effective at inhibiting tumor recurrence.

It is further submitted, with respect to claims 63-66 and 71, that none of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* disclose a method of enhancing an immune response in a subject to inhibit recurrence of a tumor using the 1D11.16 antibody, its humanized equivalent, or any anti-TGF-beta antibody, wherein the increased activity is increased tumor immunosurveillance. Thus, these references do not teach **all of the elements** of the claimed invention. Moreover, as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants' use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence (see Section (5)(i)(b) above), these references, when combined with Dasch *et al.*, similarly would not be **predictive** of the claimed method of

enhancing an immune response in a subject to inhibit recurrence of a tumor using the 1D11.16 antibody. Nor, would combining these references provide any **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an immune response in a subject to inhibit recurrence of a tumor. Accordingly, Applicants submit that claims 63-66 and 71 are allowable.

B. Rejection of Claims 46-55 and 59-72 under 35 U.S.C. § 103(a)

Claims 46-55 and 59-72 are rejected under 35 U.S.C. §103(a) are rejected as allegedly being unpatentable over Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333).

Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are discussed above (see Sections A(1) and A(5)(i)).

(i) Claims 46-55, 59, 67, and 68

Suthanthiran *et al.* discloses a "method for reducing formation or progression of neoplasms associated with immunosuppressive therapy in a mammal, the method comprising treating the mammal with an effective amount of a TGF-beta antagonist. Also provided are compositions comprising a TGF-beta antagonist and an immunosuppressive agent . . . TGF-beta antagonists of the invention include . . . anti-TGF-beta antibodies" (abstract). Thus, Suthanthiran *et al.* teaches a method of treating a subject with a combination of an anti-TGF-beta antibody and an immunosuppressive agent. Suthanthiran *et al.* also discloses the use of the 1D11.16 antibody to prevent a cyclosporine-induced increase in metastases. Suthanthiran *et al.* does not teach the use of TGF-beta antagonists, and more specifically the 1D11.16 antibody, or its humanized equivalent, to *inhibit the recurrence* of a tumor. Thus, Suthanthiran *et al.* does not, on its own, implicitly or explicitly teach **all of the elements** of the claimed methods, nor does it make up for the deficiencies of Dasch *et al.*

The February 11, 2009 Office action states that the "only difference between the instant invention and the combination of the references is the specific mention of the differen[t] types of cancers and the humanized antibo[di]es" and that TGF-beta antagonists, including monoclonal antibodies, can be used "to *treat* a variety of different cancers known to be associated with TGF-beta" (Office action at page 7, emphasis added). As discussed in Section A(2), above, the claims

are directed to a method of inhibiting (not treating) a tumor recurrence (not a primary tumor or a metastatic (secondary) tumor). Section A(4) explains that "treating" should not be equated with "inhibiting." Section A(5)(i) explains that (i) none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* is predictive of Applicants use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence and (ii) the combined teachings of these references along with Dasch *et al.* would not have led one of skill in the art to have a reasonable expectation of success that the 1D11.16 antibody would inhibit tumor recurrence. The disclosure of different types of cancers and humanized antibodies in Suthanthiran *et al.* does not improve the **predictability** of the combination of cited references nor does it contribute additional elements that would lead one of skill in the art to have a **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at inhibiting tumor recurrence. Accordingly, Applicants submit that claims 46-55, 59, 67, and 68 are allowable.

(ii) Claims 60-62, 69, and 70

It is submitted in Section A(5)(ii), above, that none of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* disclose a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody, its humanized equivalent, or any anti-TGF-beta antibody, wherein the increased activity is increased tumor immunosurveillance. Thus, these references do not teach all of the elements of the claimed invention. Moreover, as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants' use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence (see Section (5)(i)(b) above), these references, when combined with Dasch *et al.*, similarly would not be predictive of the claimed method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody. Nor, would combining these references provide any reasonable expectation of success that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an activity of an immune cell to inhibit recurrence of a tumor.

Suthanthiran *et al.* does not teach the use of TGF-beta antagonists, and more specifically the 1D11.16 antibody, or its humanized equivalent, to *inhibit the recurrence* of a tumor. Nor does Suthanthiran *et al.* disclose a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor. Thus, Suthanthiran *et al.* does not, on its own, implicitly or explicitly

teach **all of the elements** of the claimed methods, nor does it make up for the deficiencies of Dasch *et al.* In addition, the disclosure of different types of cancers and humanized antibodies in Suthanthiran *et al.* does not improve the **predictability** of the combination of cited references nor does it contribute additional elements that would lead one of skill in the art to have a **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an activity of an immune cell to inhibit recurrence of a tumor. Accordingly, Applicants submit that claims 46-55, 59, 67, and 68 are allowable.

(iii) Claims 63-66, 71, and 72

It is submitted in Section 5(A)(iii), above, that none of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* disclose a method of enhancing an immune response in a subject to inhibit recurrence of a tumor using the 1D11.16 antibody, its humanized equivalent, or any anti-TGF-beta antibody, wherein the increased activity is increased tumor immunosurveillance. Thus, these references do not teach all of the elements of the claimed invention. Moreover, as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants' use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence (see Section (5)(i)(b) above), these references, when combined with Dasch *et al.*, similarly would not be predictive of the claimed method of enhancing an immune response in a subject to inhibit recurrence of a tumor using the 1D11.16 antibody. Nor, would combining these references provide any reasonable expectation of success that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an immune response in a subject to inhibit recurrence of a tumor.

Suthanthiran *et al.* does not teach the use of TGF-beta antagonists, and more specifically the 1D11.16 antibody, or its humanized equivalent, to *inhibit the recurrence* of a tumor. Nor does Suthanthiran *et al.* disclose a method of enhancing an immune response in a subject to inhibit recurrence of a tumor. Thus, Suthanthiran *et al.* does not, on its own, implicitly or explicitly teach **all of the elements** of the claimed methods, nor does it make up for the deficiencies of Dasch *et al.* In addition, the disclosure of different types of cancers and humanized antibodies in Suthanthiran *et al.* does not improve the **predictability** of the combination of cited references nor does it contribute additional elements that would lead one of skill in the art to have a **reasonable expectation of success** that the 1D11.16 antibody or its

humanized equivalent would be effective at enhancing an immune response in a subject to inhibit recurrence of a tumor. Accordingly, Applicants submit that claims 63-66, 71, and 72 are allowable.

C. Rejection of Claims 46-72 under 35 U.S.C. § 103(a)

Claims 46-72 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of WO 00/01410, Barbera-Guillem, Rosenblum, Zavada *et al.*, and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000).

Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, and Zavada *et al.* are discussed above (see Sections A(1) and A(5)(i)).

(i) Claims 46-59, 67, and 68

The February 11, 2009 Office action states that "the only difference between the instant invention and the reference [Terabe *et al.*] is the specific mention of the specific assays used for tumor immunosurveillance" (Office action at page 9). However, this teaching is immaterial because Terabe *et al.* does not teach the use of TGF-beta antagonists (and more specifically the 1D11.16 antibody or its humanized equivalent) to *inhibit the recurrence* of a tumor. As discussed above, Dasch *et al.* does not teach methods of inhibiting tumor recurrence. Thus, Terabe *et al.* does not teach **all of the elements** of the claimed methods, nor does it make up for the deficiencies of Dasch *et al.*

As discussed in Section A(5)(i), above, (i) none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* is predictive of Applicants use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence and (ii) the combined teachings of these references along with Dasch *et al.* would not have led one of skill in the art to have a reasonable expectation of success that the 1D11.16 antibody would inhibit tumor recurrence. The disclosure of specific assays used for tumor immunosurveillance in Terabe *et al.* does not improve the **predictability** of the combination of cited references nor does it contribute additional elements that would lead one of skill in the art to have a **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at inhibiting tumor recurrence. Accordingly, Applicants submit that claims 46-59, 67, and 68 are allowable.

(ii) Claims 60-62, 69, and 70

It is submitted in Section A(5)(ii), above, that none of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* disclose a method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody, its humanized equivalent, or any anti-TGF-beta antibody, wherein the increased activity is increased tumor immunosurveillance. Thus, these references do not teach all of the elements of the claimed invention. Moreover, as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants' use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence (see Section (5)(i)(b) above), these references, when combined with Dasch *et al.*, similarly would not be predictive of the claimed method of enhancing an activity of an immune cell to inhibit recurrence of a tumor using the 1D11.16 antibody. Nor, would combining these references provide any reasonable expectation of success that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an activity of an immune cell to inhibit recurrence of a tumor.

Terabe *et al.* does not teach the use of TGF-beta antagonists, and more specifically the 1D11.16 antibody, or its humanized equivalent, to *inhibit the recurrence* of a tumor. Nor does Terabe *et al.* disclose the use of an anti-TGF-beta antibody to enhance an activity of an immune cell to inhibit recurrence of a tumor. Thus, Terabe *et al.* does not, on its own, implicitly or explicitly teach **all of the elements** of the claimed methods, nor does it make up for the deficiencies of Dasch *et al.* In addition, the disclosure of specific assays used for tumor immunosurveillance in Terabe *et al.* does not improve the **predictability** of the combination of cited references nor does it contribute additional elements that would lead one of skill in the art to have a **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an activity of an immune cell to inhibit recurrence of a tumor. Accordingly, Applicants submit that claims 60-62, 69, and 70 are allowable.

(iii) Claims 63-66, 71, and 72

It is submitted in Section 5(A)(iii), above, that none of Dasch *et al.*, WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* disclose a method of enhancing an immune response in a subject to inhibit recurrence of a tumor using the 1D11.16 antibody, its humanized equivalent, or any anti-TGF-beta antibody, wherein the increased activity is increased tumor

immunosurveillance. Thus, these references do not teach all of the elements of the claimed invention. Moreover, as none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.* are predictive of Applicants' use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence (see Section (5)(i)(b) above), these references, when combined with Dasch *et al.*, similarly would not be predictive of the claimed method of enhancing an immune response in a subject to inhibit recurrence of a tumor using the 1D11.16 antibody. Nor, would combining these references provide any reasonable expectation of success that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an immune response in a subject to inhibit recurrence of a tumor.

Terabe *et al.* does not teach the use of TGF-beta antagonists, and more specifically the 1D11.16 antibody, or its humanized equivalent, to *inhibit the recurrence* of a tumor. Nor does Terabe *et al.* disclose the use of an anti-TGF-beta antibody to enhance an immune response in a subject to inhibit recurrence of a tumor. Thus, Terabe *et al.* does not, on its own, implicitly or explicitly teach **all of the elements** of the claimed methods, nor does it make up for the deficiencies of Dasch *et al.* In addition, the disclosure of specific assays used for tumor immunosurveillance in Terabe *et al.* does not improve the **predictability** of the combination of cited references nor does it contribute additional elements that would lead one of skill in the art to have a **reasonable expectation of success** that the 1D11.16 antibody or its humanized equivalent would be effective at enhancing an immune response in a subject to inhibit recurrence of a tumor. Accordingly, Applicants submit that claims 63-66, 71, and 72 are allowable.

D. Conclusion

Applicants have shown that none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.*, Suthanthiran *et al.*, or Terabe *et al.* teach or render obvious the use of the 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence. Thus, the cited references do not make up for the deficiencies of Dasch *et al.* and, when combined with Dasch *et al.*, do not teach **all of the elements** of the claimed invention. None of the cited references is predictive of Applicants' use of the specific 1D11.16 antibody or its humanized equivalent to inhibit tumor recurrence. Thus, the combined teachings of these references and Dasch *et al.* (which does not teach inhibition, or treatment, of tumor recurrence) could not have **predictably** yielded the claimed invention. Moreover, combining the references does not provide a **reasonable**

expectation of success that the 1D11.16 antibody, or its humanized equivalent, would be effective at inhibiting tumor recurrence.

Applicants have also shown that none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.*, Suthanthiran *et al.*, or Terabe *et al.* teach the use of the 1D11.16 antibody or its humanized equivalent to enhance the activity of an immune cell to inhibit tumor recurrence. Thus, the cited references do not make up for the deficiencies of Dasch *et al.* and, when combined with Dasch *et al.*, do not teach **all of the elements** of the claimed invention. None of the cited references is predictive of Applicants' use of the specific 1D11.16 antibody or its humanized equivalent to enhance the activity of an immune cell to inhibit tumor recurrence. Thus, the combined teachings of these references and Dasch *et al.* (which does not teach inhibition, or treatment, of tumor recurrence, or enhancing the activity of an immune cell) could not have **predictably** yielded the claimed invention. Moreover, combining the references does not provide a **reasonable expectation of success** that the 1D11.16 antibody, or its humanized equivalent, would be effective at enhancing the activity of an immune cell to inhibit tumor recurrence.

Further, Applicants have also shown that none of WO 00/01410, Barbera-Guillem, Rosenblum, or Zavada *et al.*, Suthanthiran *et al.*, or Terabe *et al.* teach the use of the 1D11.16 antibody or its humanized equivalent to enhance an immune response in a subject to inhibit tumor recurrence. Thus, the cited references do not make up for the deficiencies of Dasch *et al.* and, when combined with Dasch *et al.*, do not teach **all of the elements** of the claimed invention. None of the cited references is predictive of Applicants' use of the specific 1D11.16 antibody or its humanized equivalent to enhance an immune response in a subject to inhibit tumor recurrence. Thus, the combined teachings of these references and Dasch *et al.* (which does not teach inhibition, or even treatment, of tumor recurrence, or enhancing an immune response immune in a subject) could not have **predictably** yielded the claimed invention. Moreover, combining the references does not provide a **reasonable expectation of success** that the 1D11.16 antibody, or its humanized equivalent, would be effective at enhancing an immune response in a subject to inhibit tumor recurrence.

In view of the above remarks, Applicants believe that they have overcome the rejection under 35 U.S.C. § 103(a). Applicants request that the rejection of claims 46-72 be withdrawn.

Respectfully submitted,

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Claims Appendix

1-45. (canceled)

46. (Rejected) A method of inhibiting recurrence of a tumor in a subject, comprising: administering a therapeutically effective amount of a monoclonal antibody obtained from hybridoma 1D11.16 (ATCC Accession No. HB 9849), or a humanized equivalent thereof, to the subject in order to block an immunosuppressive effect of transforming growth factor (TGF)-β in the subject, wherein the subject is at risk for recurrence of the tumor, and wherein the monoclonal antibody or humanized antibody is specific for TGF-β and neutralizes an activity of TGF-β, thereby inhibiting recurrence of the tumor in the subject.

47. (Rejected) The method of claim 46, wherein the monoclonal antibody or the humanized antibody inhibits TGF-β from binding a TGF-β receptor.

48. (Rejected) The method of claim 46, wherein the subject is a human.

49. (Rejected) The method of claim 46, wherein the tumor is benign or malignant.

50. (Rejected) The method of claim 46, wherein the tumor comprises a carcinoma, a sarcoma, a leukemia, a lymphoma, or a tumor of the nervous system.

51. (Rejected) The method of claim 46, wherein the tumor comprises a breast tumor, a liver tumor, a pancreatic tumor, a gastrointestinal tumor, a colon tumor, a uterine tumor, a ovarian tumor, a cervical tumor, a testicular tumor, a brain tumor, a skin tumor, a melanoma, a retinal tumor, a lung tumor, a kidney tumor, a bone tumor, a prostate tumor, a nasopharygeal tumor, a thryoid tumor, a leukemia, or a lymphoma.

52. (Rejected) The method of claim 46, wherein the monoclonal antibody or the humanized antibody is administered intravenously, subcutaneously, intradermally, or intramuscularly.

53. (Rejected) The method of claim 46, wherein blocking the immunosuppressive effect of the TGF-β results in increased immunosurveillance by lymphocytes of the subject.

54. (Rejected) The method of claim 53, wherein the lymphocytes comprise T cells or B cells.

55. (Rejected) The method of claim 53, wherein the lymphocytes include T cells, and the T cells comprise a cytotoxic T lymphocyte (CTL), a $CD8^+$ CTL, a $CD4^+$ cell, a $CD4^+$ CD1d-restricted T cell, an NKT cell, or a combination thereof.

56. (Rejected) The method of claim 53, wherein increased immunosurveillance is measured by an increased biological activity of the lymphocyte.

57. (Rejected) The method of claim 56, wherein the increased activity of the lymphocyte is measured by a CTL assay.

58. (Rejected) The method of claim 57, wherein the CTL assay comprises a chromium release assay.

59. (Rejected) The method of claim 46, wherein the monoclonal antibody or the humanized antibody inhibits TGF-β receptor signaling.

60. (Rejected) A method of enhancing an activity of an immune cell to inhibit recurrence of a tumor, comprising:

contacting a TGF-β receptor-expressing immune cell with an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, or a humanized equivalent thereof, wherein the monoclonal antibody or the humanized

antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased activity of the immune cell, wherein the increased activity is increased tumor immunosurveillance, thereby enhancing the activity of the immune cell to inhibit recurrence of the tumor.

61. (Rejected) The method of claim 60, wherein the TGF-β receptor-expressing immune cell is a T cell or a B cell.

62. (Rejected) The method of claim 60, wherein the TGF-β receptor-expressing immune cell includes T cells and the T cells comprise a CTL, a $CD8^+$ CTL, a $CD4^+$ cell, a $CD4^+$ CD1d-restricted T cell, or an NKT cell.

63. (Rejected) A method of enhancing an immune response in a subject to inhibit recurrence of a tumor, comprising:

administering to the subject a therapeutically effective amount of an anti-TGF-β monoclonal antibody that is obtained from hybridoma 1D11.16 having ATCC Accession No. HB 9849, or a humanized equivalent thereof, wherein the monoclonal antibody or the humanized antibody blocks a TGF-β signaling pathway and wherein blocking the TGF-β signaling pathway results in increased tumor immunosurveillance in the subject, thereby enhancing the immune response in the subject to inhibit recurrence of a tumor.

64. (Rejected) The method of claim 63, wherein the immune response is a T cell response.

65. (Rejected) The method of claim 64, wherein the T cell response comprises a CTL response, a $CD8^+$ CTL response, a $CD4^+$ T cell response, a $CD4^+$ CD1d-restricted T cell response or an NKT cell response.

66. (Rejected) The method of claim 63, wherein the subject is a human.

67. (Rejected) The method of claim 46, administering a therapeutically effective amount of the monoclonal antibody obtained from hybridoma 1D11.16.

68. (Rejected) The method of claim 46, administering a therapeutically effective amount of a humanized equivalent of the monoclonal antibody obtained from hybridoma 1D11.16.

69. (Rejected) The method of claim 60, administering a therapeutically effective amount of the monoclonal antibody obtained from hybridoma 1D11.16.

70. (Rejected) The method of claim 60, administering a therapeutically effective amount of a humanized equivalent of the monoclonal antibody obtained from hybridoma 1D11.16.

71. (Rejected) The method of claim 63, administering a therapeutically effective amount of the monoclonal antibody obtained from hybridoma 1D11.16.

72. (Rejected) The method of claim 63, administering a therapeutically effective amount of a humanized equivalent of the monoclonal antibody obtained from hybridoma 1D11.16.

Evidence Appendix

1. Dasch *et al.* (U.S. Patent No. 6,090,383); submitted and received on April 21, 2005.
2. PCT Application No. WO 00/01410; cited in the Office action dated February 11, 2009.
3. Barbera-Guillem (U.S. Patent No. 6,224,866); cited in the Office action dated November 8, 2007.
4. Rosenblum (U.S. Patent Application No. 2005/0214307); cited in the Office action dated November 8, 2007.
5. Zavada *et al.* (U.S. Patent No. 6,297,041); cited in the Office action dated November 8, 2007.
6. Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333); cited in the Office action dated June 8, 2007.
7. Terabe *et al.*, NKT cell-mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway, *Nature Immunology*, 1:515-520, 2000; submitted and received on April 21, 2005.
8. Declaration of Dr. Jay Berzofsky, dated March 10, 2008; submitted April 8, 2008 (*curriculum vitae* (referred to as Exhibit A) was inadvertently omitted from this submission, but was provided to the Office with the June 5, 2009 Declaration, submitted on June 11, 2009).
9. Declaration of Dr. Jay Berzofsky, dated June 5, 2009, accompanied by *curriculum vitae* (originally Exhibit A); submitted June 11, 2009.

Related Proceedings Appendix

There are no related proceedings.